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POLYMORPHISM AND DRUG AVAILABILITY. A REVIEW

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POLYMORPHISM AND DRUG AVAILABILITY

Drug availability is the primary concern of every individual concerned with research, design, manufacture or clinical evaluation of drugs. In the field of pharmacy, the term availity, has, however transformed into 'bioavailability' in recent years. The American Pharmaceutical Association [1] defines bioavailability as a term used to indicat measurement of both the relative amount of an administered drug that reaches the general circulation and the rate at which it occurs. Bioavailability is controlled by many factors which include the route of administration, dosage form, particle size, and methods of preparation, etc as well as physicochemical properties of the drugs.

In the field of drug design, the consideration of certain physical and chemical parameters is of prime importanc. Certain physical factors of drugs would play a great role in their bioavailability as well as pharmaceutical manufacture. Polymorphism, if not properly studied and taken into consideration, can bring about a great number of complications during the process of drug design, manufacture or its shelf life. Polymorphism is a possible complication which needs careful and prolonged studies to determine the most suitable polymorphic form for the preparation of a drug dosage form. Polymorphism has been defined by many Workers and summarized by Barth [2] as follows, "Polymorphism includes every possible difference encountered in the crystalline lattice of a substance of constant chemical composition excepting homogeneous deformations."

The polymorphic forms usually but not always belong to different crystal systems. When the change from one polymorphic form to another is reversible, it is said to be enantiotropic. When the transition takes place in one direction only

i.e., from a metstable form to a stable form the change is said to be monotropic [3].

A variety of phenomena often confused with polymorphism may be termed as pseudo-polymorphism. They include desolvation, second order transitions, dynamic isomerism and boundary migration of lattice strain effects [4].

Many substances exist in two or more crystalline forms and are said to be polymorphic. Brandstettr-Kuhnert has stated that about one in every three organic compounds exhibits polymorphic behaviour [5]. The differences are primarily in crystalline structure which give rise to difference in physical properties. The molecules of drugs exhibit different space-lattice arrangements in the crystal from one polymorph to the other, and have physical properties such as density, melting point, dissolution rate, solubility, hardness, crystal shape, crystal habit, friability and optical properties, etc. [6].

At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form and when the conversion i.e., T½ is greater than one day, the polymorph is said to be metastable rather than unstable. Metastable state is one in which equilibrium persists with respect to all but one phase. The molecules in a metastable crystal form are in a high energy level than those in the stable form of the drug, hence, the metastable form has a lower melting point and higher solubility [7].

Dissolution rates and solubilities of 3 polymorphic forms of chloramphenicol palmitate and mefanamic acid were measured [8] and it was suggested that the drugs having free energy content may significantly effect the absorption and resulting blood levels.

When the rate of conversion of a metastable form is so slow as to be negligible, the solubility of the compound will be maximal and will have a faster rate of dissolution and hence absorption. This biopharmaceutical property of the metastable polymorphs could be explained for achieving better results in the formulation of drugs, especially in the unit dosage forms of the drugs. An interesting example is that of riboflavin which exists in three metastable forms which differ in thier water solubility. The therapeutic efficacy increases with the increase in solubility [9]. the phenomenon of increased absorption has also been demonstrated by the administration of the two forms of methylprednisolone wherein *in vivo* studies of polymorphic Form II showed 1.7 times higher absorption rate than Form I and *in vitro* dissolution rate was 1.4 times higher [7].

Mesley has confirmed [10] the existence of two species of the low temperature forms (II A and II B) of sulphathiazole postulated

by Moustafa and Carless [11] and by Shenoquda [12]. Form II contains a mixture of II A with varying proportion of the other low temperature Form II B. Both Forms II A and the mixture (conveneintly called Form II) can be converted wholly to Form I by heating in an oven at about 180°C. Kuhnert-Brandstatter and Wunsch [13] stated that on long standing Form I usually reverts to the mixture of Forms II A and II B. The same phenomenon takes place in II A over a period of months. Thus it seems proble that the most stable Form of sulphathiazole is the Form II mixture. A study of 16 sulphonamides showed that 8 exhibited polymorphism [14]. Milsovich [15] stated that normal solubility determintions of sulphathiazole showed both forms I and II to have the same solubility.

Different polymorphic forms of drugs having varying and diverse nature have been prepared and utilized in the preparation of pharmaceuticals. There is a wide variety of drugs having different polymorphic forms of varying behaviour. These drugs range from prednisolone and cortisone to asprin which can be prepared in differnet polymophs by using 95 percent alcohol and n-hexane. The two forms of asprin thus produced have different melting points but the important point is that the form produced form n-hexane dissolves much more quickly.

In certain drugs, the incidence of more than two polymorphic forms is not uncommon. Out of 22 barbiturates and 16 steroids [5], studied to find out the polymorphic behaviour, 11 compounds from each class showed polymorphism. Cortisone acetate and riboflavin also showed more than 2 forms [16]. It has been concluded that there are at least two distinct polymorphic form of sulphathiazole having different lattice strutures which can be distinguished by x-ray diffraction patterns and infrared spectra. After recrystallization from different solvents four polymorphic modifications of sulphanilamide have been obtained and studied [17]. In a screening study of 16 sulphonamides [14] polymorphism was identified in eight compounds and solvates in two compounds. The p-amino group, the acidic N^1-hydrogen atom and the oxygens of the sulphonamides group were found to be involved in various hydrogen-bonding arrangements.

Amorphous & Crystalline Drugs:

A consideration of amorphous and crystalline behaviour of the drugs is also imporatant. Some drugs in addition to showing polymorphic forms may also exist in amorphous as well as crystalline forms. The energy required for a molecule of drug to leave the lattice of its crystal is more than the energy required for a molecule of drug to leave its powder. (6). As such, amorphous form of a compound is always solube than the corresponding crystalline form and therefore may exhibit different therapeutic level.

The structural units of crystalline solids are arranged in fixed geometric patterns or lattices and these units which constitute the crystal structure can be atomic, ionic or molecular. In general, based on the bonding behaviour, ionic and atomic crystals are hard and brittle having higher melting points as compared to molecular crystals which are softer and have lower melting points [18]. The very prominent examples of crystalline and characteristics in drugs are those of Novobiocin [19] and chloramphenicol palmitate [20]. Both these pharmaceutically important antibiotics when administered in crystalline form do not show effective blood levels and hence no biological activity; this is mainly due to the extremely low solubilites of the two drugs. However, their amorphous forms show reasonably good and effective results.

New compounds are sometimes obtained in crystalline forms which are metastable in nature and prove to be so in the final formulation, especially in suspension preparations. Transformations of metastable compounds to more stable forms specially in aquous preparations create considerable changes in the final formulations and cause difficulties in their manufacture. These changes taking place in the liquid preparations include growth in particle size, changes in viscocity, excessive sedimentation and cementation and as such can destroy or deteriorate the product and adversely affect the bio-availability [21].

Drugs as Solvates and Hydrates:

Some drugs when crystallized as hydrates or solvates show definite chemical composition and distinct physical properties. This may be well understood that solvates and hydrates of a compound are not and cannot be represented as the polymorphic forms of that compound. It is not correct to use the term polymorphism or crystal modification to refer to crystals of substances which just represent structures in connection with varying degrees of solvation [22].

The state of hydration of drugs can affect some physical, chemical and biological properties of drugs. More than often the anhydrous forms of an organic compound is more soluble than the hydrate. Anhydrous and trihydrate forms of ampicillin were studied [23] on dogs as suspension and capsules. The results showed that anhydrous form had better absorption and greater bioavailability than the trihydrate. The hydrates or solvates of such drugs would show comparatively much lesser *in vivo* absorption and *in vitro* dissolution. Prednisolone tert butyl acetate [24] when compressed is tablets and implanted subcutaneously in rats showed the difference between the anhydrous and monoethanol solvate. The solvate showed 4 times higher absorption rate in the animals. A 13.4 percent ethanol-water,

mitxture was used to obtain hydarted form of glutethimide having melting point of 68C and was compared with the anhydrous drug having melting point of 83C. For the *in vitro* dissolution behaviour, the anhydrous form was 1.6 times faster in its dissolution as compared to the hydrate [21].

Thermodynamic relationships of methyl prednisolone involving polymrphism and solubility were examined [25] in water, decyl alcohol and dodecyl alcohol at vorious temperatures. The two forms showed independent solubility ratios in respect of solvents. At room temperatures the activity of the more energetic form II of the drug was found to be about 80 percent greater than that of the more stable form I.

EFFECT OF POLYMORPHISM IN PHARMACEUTICAL PREPARATIONS

(a) Chemical stability:

Different crystalline Phases of the same compound have different chemical stabilities. Corticosteroid suspenstons when industrially prepared showed batch to batch difference in their stability. However, an x-ray differaction analysis of the starting raw material disclosed the polymorphic differences and explained the stability behaviour which could be due to the solvents occluded or the absorbed mother liquor [26].

Crystalline potassum penicillin can withstand dry heat for quite some time without considerable decomoposition but amorphous type looses its activity to quite an extent. This property is very important in preparation which require penicillin to be coated or deposited. Penicillin suspension prepared with crystalline powder would be in a much finer state of sub-division with greater stability than those prepared with amorphous powder.

(b) Tablet Compression :

Polymorphism is a function of internal structure of crystals whereas the outer apparance of a crystal is termed as its habit. In the compression of tablets when the major portion or bulk of a formulation is the active ingredient, then all other conditions being equal, the correct choice of right polymorph is the one with a habit that can be compressed easily into tablet form. Different habits of the same compound can create hurdles in each batch when the habit of the drug chaiges [27].

(c) Particle Size :

Polymorphism can be used in pharmaceutical industry in the preparation of fine particles by using the density difference for enantiotropic polymorph. Different polymorphs of the same compound have different densities and so when one polymorphic form is heated above its conversion temperature to

form another polymorph, strains will be developed in this later polymorphic form on cooling to room temperature. The strains produced in the crystal give rise to fracturing into finer perticles. This operation will hold good only when suitable polymorphic forms do exist in a compound and also when repeated temperature cycling would not produce chemical degradation. This method can in certain instances be even more useful and preferenticl over micronization [4].

(d) Polymerization :

Tributylvinylphosphonium [28] bromide exists in three phases out of which phase II is metastable and polymerizes faster than the other two phases. The rapid polymerization is due to steric and collision factors which are governed by crystaline structures.

(e) Suppositories :

Polymorphic changes of a supporting base can lead to absolutely unfit preparation impossible to be used because of its melting behaviour which is the most important characteristic of the suppositories. Theobroma oil which is the most popular and widely used supporting base has three unstable forms which melt at 18, 22 & 28°C and one stable form melting at 34.5°C. An ultimate transformation of unstable form to stable form may take place if the suppositories are left in the moulds for few days. Unnecessary heating of the base at relatively higher temperature and ultimate immediate chilling causes the unstable form to appear. Suppositories so prepared will melt at about 39°C. The overheating of the oil also causes se limentation of the active ingredient and excessive contraction on chilling bearing a depression in the product. Properly heating the base only a few degrees above its melting point (34.5C) and congealing permits the crystallization nuclei of the m re stable, higher and suitable form crystals to remain in the liquid. This on chilling encourages further crystallization of crystals [21].

(f) Parenteral Preparations :

The polymorphic behaviour of drugs also plays a big role in the absorption rates of parenteral preparations. The differences in water solubilities cause pronounced effects on the absorption rates an l change the entire expected bioavailability. Examples of compounds like methylprednisolone, glutethimide, novobiocin, ampicillin and different hormones have been cited invariably wherein polymorphism plays a big role. Crystal growth not only effects the oral preparations but can also cause difficulties in parenteral products specially the problem of syringability.

(g) Solution & Mi tures :

In solution or mixture type of pharmaceuticals, the primary consideration should be to determine the solubility of the drug in the vehicle. A thermodynamically unstable formulation will result if a metastable form

of the drug is used and if the quantity of the drug in the system exceeds the equilibrium. Solubility determinations for this class of preparations should be made with a most stable as well as most soluble form The most soluble form may not necessarily be most stable. Chance nucleation of the stable form may however quickly result in recrystallization. Steroidal drugs which are sparingly water soluble frequently cause such problems. These problems [4] can be minimised by formulating the drug with a suitable cosolvent.

(b) Creams Suspensions :

Certain suspensions of cortisone acetate polymorphs were prepared and it was found that a physically stable aqueous suspension is difficult to make ; crystal growth of the durg occured invariably with subsequent caking and sedimentation.

Polymorphic behaviour in the case of pharmaceutical creams is not very different from that of suspensions wherein a phase inversion takes place from that of metastable to a stable form resulting in crystal growth and the vehicle yielding gritty unacceptable cream. Unevenly distributed active ingredient proves that an undesirable polymorphic form of the drug has been used. The best method to avoid such a performance is to choose the polymorphic phase which is least souible in the base. However, if the phase conversion is very slow, a more soluble, metastable form can safely be used.

The *transformation from metastable to* stable form is a rather tricky point and can only be detected through or thorough and complete study of product formulation and stability. They are difficult to predict in the earlier stages and can be detected after x-ray differaction, hot stage microscopy, differential thermal analysis and other appropriate techniques.

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